Invasive Zygomycosis in Hematopoietic Stem Cell Transplant Recipients Receiving Voriconazole Prophylaxis

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(See the editorial commentary by Kauffman on pages 588–90)

We report 4 cases of invasive zygomycosis in hematopoietic stem cell transplant recipients, all occurring after May 2003, when voriconazole began to be used as antifungal prophylaxis. No cases of zygomycosis had been detected in this population in the 3 years prior to May 2003. All 4 patients were receiving immunosuppressive therapy for presumed graft-versus-host disease. Profoundly immunosuppressed patients receiving voriconazole prophylaxis remain at risk for less-common pathogens that are intrinsically resistant to this agent.

The Infectious Diseases Society of America guidelines recommend fluconazole prophylaxis for allogeneic hematopoietic stem cell transplant (HSCT) recipients to prevent invasive candidiasis [1–3]. But because fluconazole has little activity against filamentous fungi, including Aspergillus species, infections with these pathogens continue to increase in frequency [4]. Voriconazole is known to have excellent activity against both Aspergillus species and most Candida species, so some HSCT centers now prefer to use voriconazole as prophylaxis, an approach that has not yet been rigorously evaluated in a clinical trial. Although voriconazole has a broad spectrum of antifungal activity, it has poor in vitro activity against the zygomycetes [5]. It is therefore notable that one group of investigators has reported a small series of HSCT recipients receiving voriconazole prophylaxis who developed zygomycosis [6]. We report 4 cases of invasive zygomycosis that have occurred in our HSCT population since we began to use voriconazole as prophylaxis.

Case reports. Patient 1 was a diabetic man in his early 50’s who received an allogeneic, T cell–depleted, matched unrelated HSCT for myelodysplastic syndrome. Voriconazole prophylaxis (200 mg po b.i.d.) was begun 7 days prior to transplantation. After undergoing transplantation, the patient developed a neutropenic fever and was treated with levofloxacin and meropenem. His fevers persisted, and the voriconazole dose was increased to 400 mg. CT scans of the chest and sinuses were unremarkable. The patient then developed a desquamating rash on his scalp and scrotum, his bilirubin levels increased, and he developed watery diarrhea that became bloody. His voriconazole dosing was changed from oral to intravenous, and he was given steroids for presumed graft-versus-host disease (GVHD). He did not improve, and a 5-day course of antithymocyte globulin was initiated. His mental status worsened, his fever persisted, and he died after a bradycardic episode on day 27 after transplantation.

An autopsy revealed thickened walls of the pulmonary vessels with several organized thrombi. Within the thrombi and the surrounding lung were branching, aseptate hyphae consistent with a zygomycete. Microscopic examination of sections of the stomach and intestine also revealed many fungal forms consistent with zygomycetes (figure 1A).

Patient 2 was a woman in her late 20’s who received an allogeneic, T cell–depleted, matched unrelated HSCT for recurrent lymphocyte-depleted Hodgkin lymphoma. She had experienced transplantation failure after receiving a prior autologous transplant. She received voriconazole (200 mg po b.i.d.) on initiation of the conditioning regimen. She continued to receive this dosage of voriconazole until her death (although oral dosing was changed to intravenous dosing when she developed gastrointestinal symptoms). She developed a fever while neutropenic, and treatment with levofloxacin and aztreonam was started. She recovered from neutropenia, but she then developed bloody diarrhea, fever, and a maculopapular skin rash. Findings of a sigmoid biopsy were consistent with GVHD. She received mycophenolate mofetil (MMF), methylprednisolone, and cyclosporin; had persistent bloody diarrhea; and began to receive antithymocyte globulin. She then developed left hemiparesis, and a pons infarct was seen by MRI. She became unresponsive, and her family decided to withdraw care on day 70 after her transplantation.
Figure 1. Representative photomicrographs of tissue from each patient (original magnification, ×40). A, Patient 1: a section of tissue from the small intestine (gomez methenamine silver [GMS] stain). B, Patient 2: a section of tissue from a pulmonary blood vessel (periodic acid-Schiff stain). C, Patient 3: a section of tissue from the upper left lobe of the lung (GMS stain). D, Patient 4: a section of lung tissue demonstrating sporangia and sporangiophores (hematoxylin and eosin stain).

Her autopsy revealed multiple thrombi, including fungal elements with aseptate hyphae consistent with a zygomycete, in the lungs, liver, ovary, and bladder (figure 1B). A large proximal portal vein branch was occluded by a fungal thrombus. A marantic vegetation was noted on the mitral valve, and the pons showed necrosis without evidence of fungal forms.

Patient 3 was a woman in her early 50’s with relapsed follicular small-cleaved cell lymphoma who underwent allogeneic, unrelated peripheral blood stem cell transplantation with use of a low intensity regimen that consisted of fludarabine and melphalan. The graft was treated in vitro with alemtuzumab. Prior to receiving the transplant, the patient began to receive therapy with voriconazole (200 mg po b.i.d.). On day 5 after transplantation, vancomycin and piperacillin-tazobactam were added to the regimen to treat fever and erythema around her port. She experienced resolution of neutropenia after 2 weeks. The patient’s fever resolved, and the antibacterial agents were discontinued, but voriconazole was continued. On day 16 after transplantation, the patient developed pleuritic chest pain, and a CT scan of the chest showed a peripheral nodule 2.2 cm in diameter. Her voriconazole dosage was then increased to 300 mg po b.i.d. She developed a skin rash and had elevated liver function test values, and she began to receive solumedrol and MMF for presumed GVHD. On day 60, she again had pleuritic chest pain and worsening dyspnea, and a second CT scan of the chest revealed patchy airspace disease. She had progressive dyspnea, and life support was removed on day 68 after transplantation. One week prior to the patient’s death, a surveillance stool culture grew 1 colony of *Rhizopus* species.

An autopsy limited to the patient’s lungs revealed multiple pulmonary emboli in her left lung, with invasive aseptate hyphae consistent with a zygomycete (figure 1C). Cultures grew a *Rhizopus* species.

Patient 4 was a woman in her late 50’s with relapsed acute myelogenous leukemia (M2) who was admitted to the hospital to receive an allogeneic HSCT. She began to receive voriconazole prophylaxis (200 mg po b.i.d.) at the time of the transplantation. She developed a neutropenic fever and was treated with levofloxacin, aztreonam, and vancomycin. She received cyclosporin and MMF to prevent GVHD, was discharged from the hospital 18 days after receiving the transplantation, and was treated with voriconazole (200 mg q.d). Because of neutropenia and a progressive decrease in donor chimerism, she received 7.5 × 10⁵ CD3⁺ cells/kg on day 133 after transplantation. One
month later, she developed fever, diarrhea, and a maculopapular rash over her upper chest, arms, and legs. A rectal biopsy revealed grade 4 GVHD. Solumedrol (1 mg/kg b.i.d.) and cyclosporine were added to the regimen. On day 167 after transplantation, Candida albicans was cultured from samples of the patient’s blood, and the dosage of voriconazole was increased to 270 mg iv b.i.d. (3 mg/kg). After 4 days of increased immunosuppression without any improvement, atg (30 mg/kg per day for 5 days) was added to the regimen. On day 185 after transplantation, the patient underwent a CT scan of the chest that revealed multiple wedge-shaped infarcts consistent with fungal pneumonia. Her mental status decreased rapidly, and she died on day 187 after transplantation.

Her autopsy revealed widespread zygomycete forms throughout her lungs. Fungal nodules were observed, with invasion into bronchi and pulmonary vessels. Sporangiospores were widespread throughout the lungs (figure 1D). Her gastrointestinal tract showed changes consistent with GVHD and viral inclusions consistent with cytomegalovirus infection.

Discussion. Infections due to fungi of the class Zygomycetes are rare, occurring at an annual rate of 1.7 cases per million population in the United States [7]. The most common clinically significant genera in this group include Macuor, Rhizopus, Rhizomucor, and Absidia species. Zygomycetes are classically associated with rhinocerebral and pulmonary disease in humans, but case reports have documented cutaneous, gastrointestinal, and disseminated infections, as well [8–10]. Patients at risk include those with diabetic ketoacidosis, hematologic malignancies, deferoxamine therapy, burn wounds, and long-term prednisone use. Culture results are often negative, and there are no readily available immunologic or molecular markers, so diagnosis usually requires histopathologic examination. Effective therapy is also challenging and involves surgical debridement, high-dose amphotericin B, and correction of underlying immunodeficiencies [11]. Recent data suggest that the experimental triazole antifungal agent posaconazole may have useful activity against some zygomycetes [12–14].

A review of zygomycosis from The M. D. Anderson Cancer Center (Houston, TX) [15] revealed that, from 1989 through 1998, ten (0.25%) of 4020 hematopoietic stem cell transplantations were complicated by zygomycosis. In their review of all patients who developed invasive zygomycosis were receiving antifungal prophylaxis, most commonly with fluconazole or itraconazole.

Our institution has seen an increase in the incidence of invasive zygomycosis corresponding to an increase in the use of voriconazole prophylaxis in HSCT recipients. Since May 2003, when voriconazole prophylaxis was begun, 45 transplantations have been performed. Of these 45 cases, 4 (8.9%) involved documented invasive zygomycosis. In the preceding 3 years, during which itraconazole (or fluconazole, for patients who did not tolerate itraconazole) was used for prophylaxis, our institution had no documented cases of zygomycosis in HSCT recipients. No other major changes in practice or environment occurred in our HSCT population coincident with this change in prophylaxis, and an outbreak investigation (including environmental evaluation and culturing) has not revealed a point source for these infections.

Prior to May 2003, invasive aspergillosis (IA) was the most common fungal infection in our HSCT population, with 3 years of surveillance revealing a cumulative incidence of proven or probable IA of 12% (data not shown). Since May 2003, three (6.6%) of the 45 HSCT recipients have received a diagnosis of IA, and none of them received voriconazole prophylaxis (in each case, voriconazole was discontinued prior to transplantation because of drug intolerance).

This experience raises concern regarding broad use of any antifungal agent in this high-risk population. The organism with the greatest intrinsic resistance to the antifungal employed may ultimately emerge as a cause of infection in the most vulnerable patients. Because the diagnosis of invasive zygomycosis is challenging, the diagnosis is often not suspected during a patient’s life—and because autopsy rates are decreasing, the infection may never be recognized. This points to the importance of developing new, non-culture based diagnostic methods for invasive fungal pathogens [16]. We report our experience in the hope that other centers will carefully evaluate the changing epidemiology of invasive fungal infections as practices change regarding the use of antifungals. Further study should utilize data from ongoing multicenter studies of invasive fungal infections in transplant recipients (e.g., the TRANSNET study [17]), including case-control studies, to evaluate risk factors associated with use of antifungals for the development of zygomycosis and other less common fungal infections.

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